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7590 03/26/2003  
Arnold White & Durkee  
1900 One American Center  
600 Congress Avenue  
Austin, TX 78701-3248

EXAMINER

HUYNH, PHUONG N

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1644

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18

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/576,101

Applicant(s)

SUHRBIER ET AL.

Examiner

" Neon" Phuong Huynh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 25 November 2002.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 14-34 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 14-34 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 November 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

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### DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/25/02 has been entered.
2. Claims 14-34 are pending and being acted upon in this Office Action.
3. The disclosure is objected to because of the following informalities: "Figure 6" and "Figure 8" in the Brief Description of drawing on page 5 is no longer match with the newly submitted Figure 6A-6J and Figure 8a-8c, respectively. Further, it is noted there is inconsistency in the labeling of Figures 8a-c and 9a-j (regular letter) and Figures 6A-6J (capital letter). Appropriate action is required.
4. The following is a quotation of the first paragraph of 35 U.S.C. 112:  
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
5. Claims 14-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant vaccine CTL polypeptide-based composition comprising a polynucleotide encoding CTL epitopes as depicted in Figure 5 derived from pathogens MCMV, influenza, EBV, Adenovirus and EG7 tumor for use as vaccines, does not reasonably provide enablement for vaccine compositions and their use in vaccination against *any* HIV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable

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one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a polynucleotide comprising multiple (up to ten) murine CTL epitope as depicted in Figure 5 from pathogens listed in Table 2 on page 14 in which the pathogens are from Epstein Barr Virus, Influenza virus, Cytomegalovirus, and Adenovirus. The response to said CTL epitopes from different pathogens are restricted by individual's HLA class where said CTL epitopes are linked contiguously to a T helper cell epitope from Ovalbumin and a B cell epitope from plasmodium falciparum in a linear fashion (See Fig 5, in particular) that expressed in vaccinia virus vectors and uses to vaccinate mice against MCMV, influenza, EBV and EG7 tumor.

The specification does not teach how to make and use any polynucleotide comprising any nucleic acid sequence encoding *any* CTL epitopes from HIV that can use in a recombinant nucleic vaccine against HIV infection. The specification does not disclose how using a recombinant vaccinia vector containing a polynucleotide encoding CTL epitopes from Influenza, EBV, Cytomegalovirus, Adenovirus and EG7 tumor can be extrapolated to protect HIV infection. Further, there is insufficient evidence that nucleic acid (DNA) vaccine using CTL epitopes from Influenza, EBV, Cytomegalovirus as depicted in Fig. 5 can prevent AIDS and against HIV infection. Applicants have not disclosed *any* "CTL epitopes" from HIV other than **murine** CTL epitopes from Epstein Barr Virus, Influenza Virus, Cytomegalovirus and Adenovirus depicted in Fig. 5 and listed in Table 2, in turn, can be used as a vaccine against HIV infection. The claimed invention of "Nucleic acid vaccine" as recited in claim 33-34 comprising any polynucleotide comprising any nucleic encoding any plurality of CTL epitopes, much less prevention of any disease. A polynucleotide or nucleic acid vaccine comprising polynucleotide without SEQ ID NO has no structure, much less function, in turn would be useful as a vaccine against any disease. Further, there is insufficient guidance and working examples at the time the application was filed that any undisclosed nucleotide encoding any undisclosed CTL epitopes is effective for a vaccine against a plurality of pathogens such as HIV. Reasonable correlation must exist between the scope of the claims and scope of enablement.

The specification has not enabled the breadth of the claimed invention in view of the teachings in the specification as filed. The lack of guidance in the specification as to which CTL epitopes from HIV are appropriate for nucleic acid vaccine against HIV infection is unpredictable

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and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The state of the art is such that even though HIV vaccine research has been under way for 10 years, not a single vaccine has been demonstrated to be effective against AIDS (See page 1993 col. 3, last two paragraph, JAMA 282 (21): 1992-1994; PTO 892). Ramsay *et al* summarizes that "vaccine involving proteins or whole inactivated virions have not, to date, reliably induced either antibodies capable of neutralizing HIV or CTL responses, in human or non-human primates and for reasons which remain unclear, even DNA vaccines do not appear to reliably induce CTL response in outbred primates" including humans (see page 31 column 2, in particular).

Verma *et al*, of record, teach that the problem of gene therapy is the inability to deliver genes efficiently to the right type of cell, obtaining sustained expression of the therapeutic protein and without triggering the host immune responses (See page 239, in particular). Therefore, in the absence of in vivo working examples, it would require undue experimentation of one skilled in the art to practice the claimed invention.

Reyes-Sandoval *et al*, of record, teach that "Although DNA vaccines induce significant immune responses in small animal trials their efficacy in humans has so far been less promising thus necessitating additional optimizations of this novel vaccine approach".

Tuteja *et al*, of record, teach that "There are several hurdles that need to be overcome on the road to the use of DNA vaccines widely. These include the technical challenges of improving delivery and/or potency so that low doses of DNA can achieve the efficacy of conventional vaccines.

In view of the insufficient number of working examples, the lack of guidance in the specification, the breadth of the claims, and the unpredictable state of the art with respect to *DNA vaccine* against a plurality of undisclosed pathogens such as HIV, it would require undue experimentation for one skilled in the art to practice the entire **scope** of the claimed invention.

Applicants' arguments filed 11/25/02 in conjunction with the Declaration of Andreas Suhrbrier have been fully considered but are not found persuasive.

Applicants' position is that (1) the declaration of Andreas Suhrbrier attested to the fact that the polynucleotide has additional uses such as the generation and monitoring of CTL responses. (2) Several US patents have been granted for isolated HIV-1 CTL epitope peptides on application filed before the priority date of the instant application such as US Pat No. 5,700,635 to McMichael, US Pat No 5,932,218 to Berzofsky et al and US Pat No. 6,294,322 to Berzofsky et

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al. (3) It is incorrect to assume that the only disclosed utility for the subject polynucleotide constructs is as a vaccine because the specification clearly discloses other uses such as CTL assays, and the enhancement of CTL response (page 8, lines 13 to page 9, line 34 of specification). The specification discloses at page 14 line 8 to 13 the use of mouse polypeptide to induce primary CTL response in mice. (4) At the priority date of instant application, it is routine at the priority date to provide functional CTL epitopes for inclusion in a polypeptide produced in accordance with the present invention. (5) Paragraph 33 of the Suhrbier Declaration exemplifying several polypeptides produced according to the teaching provided in the specification. (6) With regard to claims 33 and 34, the Suhrbier declaration which relates that "Gardner et al teach a polypeptide construct encoding multiple tandem HIV HLA A- restricted CTL epitopes (Table 1), its delivery by modified vaccinia virus Ankara (MVA), and the testing of same in HLA A2 transgenic mice prior to human clinical trials (page 296 "Polytope vaccines against HIV/AIDS"). Gardner et al state at page 296, lines 1-5 that the "polytope approach has now been shown to work for a variety of epitopes, disease and vectors including HIV and modified Vaccinia Ankara (MVA). (7) The Declaration of Mr. John Cooper Cox at paragraph 41 states that "given the plethora of known CTL epitopes from HIV at the filing date of the present application, and from the teaching provided that individual CTL epitopes are correctly processed and presented from the claimed polypeptide formulation. It would be routine matter to substitute the exemplified CTL epitopes proved by the inventors with other CTL epitopes, specially known HIV-1 CTL epitopes".

Contrary to Applicant's assertion that polypeptide vaccine in instant application is for monitoring CTL responses, the title of instant specification, as well as the summary of the specification on page 2 at lines 23 bridging page 3 disclose that the polypeptide proteins and the corresponding polypeptide polynucleotides are intended for use as a vaccine.

In response to Applicant's argument that several US patents have been granted for isolated HIV-1 CTL epitope peptides on application filed before the priority date of the instant application to uses other than vaccines, every case is examined on its own merits. Further, none of these patents are drawn to HIV vaccine as pointed out at paragraph 15 in the Declaration of Andreas Suhrbier.

In response to Applicant's argument that the specification clearly discloses other uses such as CTL assays, and the enhancement of CTL response, the page 8, line 13 to page 9, line 34 of specification as pointed out by Applicant, the CTL assays and enhancement of CTL response

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are not the subjects of Applicant's invention as evidence by the cited references of record. Further, at page 8, the specification discloses that CTL assay is used to see whether each epitope could be efficiently process from the polytope protein using autologous CTL clones. Again, the specification on page 15 at line 5 clearly discloses that the multiple CTL epitope in the polytope is vaccine... to prevent disease progression.

In response to Applicant's argument that it was routine at the time of filing that isolating CTL epitopes and determining its structure and function is routine, the claims, however, are not drawn to methods of screening for CTL epitope. The claims are drawn to synthetic or recombinant protein comprising a plurality of any CTL epitope for use as a vaccine to prevent disease progression. It is not routine to make vaccine comprising any CTL epitopes for preventing any disease progression such as HIV.

In response to Applicant's argument that examples 1 and 2 provide in vivo working examples of polyepitope polypeptides construct having human HLA restriction, the specification does not teach how to make and use any synthetic or recombinant protein comprising any CTL epitopes from pathogen such as HIV that can be use in a recombinant protein vaccine against HIV infection, much less for preventing any disease progression. The specification merely mentions CTL epitope from HIV. The specification does not actually discloses the specific amino acids of any CTL epitope from HIV, the corresponding nucleotide sequence, in turn, for polyepitope vaccine against HIV. There is insufficient guidance as how to extrapolate nucleic acid vaccine or polynucleotide comprising any nucleic acid sequence encoding CTL epitopes from Influenza, EBV, Cytomegalovirus, Adenovirus and EG7 tumor to protect HIV infection. Further, there is insufficient in vivo working demonstrating that any nucleotide comprising any nucleic acid sequence encoding a plurality of CTL epitopes from Influenza, EBV, and Cytomegalovirus as depicted in Fig. 5 can prevent AIDS due to HIV infection. Applicants have not disclosed *any* "CTL epitopes" from HIV other than **murine** CTL epitopes from Epstein Barr Virus, Influenza Virus, Cytomegalovirus and Adenovirus depicted in Fig. 5 and listed in Table 2, which, in turn, can be used as a vaccine against HIV infection. Even if the CTL epitope from HIV are disclosed, in vitro cytotoxic assays do not necessary correlate with prevention of HIV infection in vivo. Thus the claimed invention of "a polyepitope vaccine comprising any synthetic or any recombinant protein comprising a plurality of *any* CTL epitopes against *any* "a plurality of pathogens", including "HIV" is broad and not enabled.

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In response to Suhrbier's Declaration that CTL epitopes from HIV are known before the filing date of the present application (paragraph 23) and polypeptides produced according to the teaching provided in the specification, the specification does not have a statement to the effect that CTL epitope in the prior art are incorporated by references at the time the application was filed. The specification merely mentions CTL epitope from HIV. The specification does not actually disclose the specific amino acids of any CTL epitope from HIV, the corresponding nucleotide sequence, in turn, for polypeptide vaccine against HIV. There is insufficient guidance as how to extrapolate nucleic acid vaccine or polynucleotide comprising any nucleic acid sequence encoding CTL epitopes from Influenza, EBV, Cytomegalovirus, Adenovirus and EG7 tumor to protect HIV infection. More importantly, there is no *in vivo* working example demonstrating any polynucleotide encoding any CTL epitope would prevent HIV infection.

In response to Applicant's argument in conjunction with the Suhrbier declaration at paragraph 34 to 37 on vaccine, the example 2 in the specification discloses only murine CTL epitopes as depicted in Figure 5 from pathogens listed in Table 2 on page 14 of specification, which are Epstein Barr Virus, Influenza virus, Cytomegalovirus, and Adenovirus. The specification discloses on page 14 that each epitope in the polypeptide induces primary CTL response with the appropriate MHC allele. Other than the specific CTL epitopes from the specific pathogens, there is insufficient guidance and working example that the same nucleic acid sequence encoding a plurality of CTL epitopes is efficacious for preventing HIV infection. The claims as written encompass any nucleic acid vaccine comprising a nucleic acid sequence encoding a plurality of pathogens such as at least three, four, nine or ten of any CTL epitopes contiguous or spaced apart by any undisclosed intervening sequence that does not "comprise" a methionine and an acceptable carrier for preventing any disease. Further, the term "comprising" or "comprise" is open-ended. It expands the polynucleotide to include additional nucleotide at either or both ends in addition to any undisclosed CTL epitope encoded by said polynucleotide. Given the lack of guidance as to the structure of any polynucleotide comprising any nucleic acid sequence encoding any plurality of CTL, it follows any nucleotide encoding a plurality of CTL epitopes from any pathogen for use as a vaccine such as HIV or CTL epitope assay is not enabled.

Claims 33-34 are drawn to a nucleic acid vaccine comprising a polynucleotide comprising any nucleic acid sequence encoding (i) a plurality of undisclosed CTL epitopes wherein each CTL epitope is substantially free of peptide sequences naturally found to flank that



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CTL epitope and wherein at least two of the plurality of CTL epitopes are contiguous or spaced apart by any undisclosed intervening sequence that does not comprise a methionine and (ii) an acceptable carrier. There is insufficient guidance as to the structure of any nucleic acid mentioned above, let alone vaccine for preventing any disease. The specification does not teach any CTL epitopes from any pathogens such as HIV, the corresponding polynucleotide for said CTL epitope for a vaccine. Further, there is no guidance as to the structure of any intervening sequence. The term "comprising" or "comprise" is open-ended. It expands the polynucleotide encoding a plurality of undisclosed CTL epitopes and intervening sequence to include additional nucleotide at either or both ends. A vaccine by definition is for prevention of a particular disease. Given the indefinite number of undisclosed polynucleotide encoding the undisclosed CTL epitope from indefinite number of pathogens, there is insufficient in vivo working example that any undisclosed polynucleotide or any nucleic acid vaccine is efficacious for preventing any disease such as HIV infection. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Given the indefinite number of undisclosed polynucleotide and nucleic acid vaccine, the specification does not adequately teach how to effectively prevent any disease such as AIDS by administering the recombinant protein encoded by the polynucleotide construct as shown in Figure 5 commensurate in scope with the claimed invention. It is not clear that the skilled artisan could predict the efficacy of the any polynucleotide as exemplified in the specification and the breadth of any nucleic acid vaccine encompassed by the claims. Even if the nucleic acid vaccine is limited to the ones in Fig 5 and Table 2, there is insufficient guidance as to the specific CTL from pathogen such as HIV that the nucleic acid vaccine supposes to prevent. Clearly further research would be required. See *Brenner v. Manson*, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment.

6. Claims 14-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is

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whether that description "reasonably convey to the artisan that the inventor had possession at the time of the ... claimed subject matter", *Vas-Cath, Inc. V. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicants had possession at the time of invention of the claimed polynucleotides and the nucleic acid vaccine recited in claims 14-34. The nucleic acid sequences recited in claims 14-34 encompass a large genus of polynucleotides and vaccines. There is insufficient disclosure in the specification to reasonably convey to the artisan that the inventors had possession of the claimed invention.

Applicant has described only a polynucleotide encoding multiple murine CTL epitopes from murine Cytomegalovirus, lymphocytic choriomeningitis, influenza, EBV, Adenovirus, T helper cell epitopes from *Berghia circumsporoite* and Ovalbumin, and B cell epitopes from *plasmodium falciparum* as disclosed in Table 2 expressed in a vaccinia viral vector depicted in Fig. 5. The specification further discloses that the CTL epitopes are arranged in tandem in a contiguous sequence and the said CTL epitopes are from **different** HLA alleles flanking by a B cell epitope from *plasmodium falciparum* (See Fig 5, in particular). The arrangement of the ten CTL epitopes within the construct is such that two CTL epitopes in tandem are from the same MHC class I HLA alleles but from different pathogens (See Figure 5 and Table 2, in particular). The specification as filed does not adequately describe the claimed genus, which encompasses CTL epitopes other than the one depicted in Fig. 5 and listed in Table 2 such that one skilled in the art would conclude that applicants were in possession of the claimed invention.

With the exception of the specific polynucleotide encoding the specific CTL epitopes mentioned above for CTL assay, there is insufficient written description about the structure associated with function of *any* polynucleotide comprising any nucleic acid sequence encoding a plurality of undisclosed CTL epitopes wherein each CTL epitope is substantially free of peptide sequences naturally found to flank that CTL epitope and wherein at least any two of the plurality of any CTL epitopes are contiguous or spaced apart by any intervening sequence that does not comprises a methionine because any polynucleotide without the specific nucleic acid sequence or SEQ ID NO has no structure, much less function, in turn, would be useful as a nucleic acid vaccine against any pathogen such as AIDS. Since the polynucleotide encoding any undisclosed CTL epitopes is inadequately described, it follows that any vector comprising any undisclosed polynucleotide is not adequately described. It also follows that any nucleic acid vaccine is not adequately described.

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Further, the specification discloses only polynucleotide encoding multiple murine CTL epitopes from murine Cytomegalovirus, lymphocytic choriomeningitis, influenza, EBV, Adenovirus, T helper cell epitopes from *Berghei circumsporozoite* and Ovalbumin, and B cell epitopes from *plasmodium falciparum* as disclosed in Table 2 expressed in a vaccinia viral vector as depicted in Fig. 5, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus as broadly claimed. See *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 11/25/02 in conjunction with the Declaration of Andreas Suhrbrier have been fully considered but are not found persuasive.

Applicants' position is that (1) CTL epitopes are recognized by one of skill in the art of immunology. (2) the specification described more than a sufficient number of representatives of the genus of CTL epitopes within the context of the methods of the invention so as to demonstrate that they have fully set forth and possesses the invention. (3) The enclosed Cox Declaration and Exhibits JCC1 through JCC17 in Appendix F provide objective evidence that the specification as filed contains sufficient representative examples to demonstrate that a skilled person that the inventors actually invented what they now claim.

In response, The specification discloses only a polynucleotide encoding multiple murine CTL epitopes from murine Cytomegalovirus, lymphocytic choriomeningitis, influenza, EBV, Adenovirus, T helper cell epitopes from *Berghei circumsporozoite* and Ovalbumin, and B cell epitopes from *plasmodium falciparum* as disclosed in Table 2 expressed in a vaccinia viral vector depicted in Fig. 5. The specification further discloses that the CTL epitopes are arranged in tandem in a contiguous sequence and the said CTL epitopes are from **different** HLA alleles flanking by a B cell epitope from *plasmodium falciparum* (See Fig 5, in particular). The arrangement of the ten CTL epitopes within the construct is such that two CTL epitopes in tandem are from the same MHC class I HLA alleles but from different pathogens (See Figure 5 and Table 2, in particular). With the exception of the specific polynucleotide encoding the specific CTL epitopes mentioned above, there is insufficient written description about the structure associated with function of *any* polynucleotide comprising any nucleic acid sequence

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encoding a plurality of undisclosed CTL epitopes wherein each CTL epitope is substantially free of peptide sequences naturally found to flank that CTL epitope and wherein at least any two of the plurality of any CTL epitopes are contiguous or spaced apart by any intervening sequence that does not comprises a methionine because any nucleic acid without the nucleotide sequence or SEQ ID NO has no structure, much less function. Further, the term "comprising" or "comprises" is open-ended. There is insufficient written description about the nucleotide to be added to the undisclosed polynucleotide in addition to the nucleotide to be added to the undisclosed intervening sequence so long the intervening sequence does not contain a methionine. Since the polynucleotide encoding any CTL epitopes is inadequately described, it follows that any vector, any nucleic acid vaccine comprising any undisclosed polynucleotide is not adequately described.

The issue here is not one of skill in the art of immunology would know how to identify CTL epitopes or do CTL assays. Although some CTL epitopes are already known in the literature at the time the invention as filed, not all CTL epitopes whether it is disclosed or undisclosed are useful for a vaccine. Even if the nucleic acid vaccine is limited to the ones in Fig 5 and Table 2, there is insufficient written description about the CTL epitope from the specific pathogen such as HIV that the nucleic acid vaccine suppose to prevent.

In response to Applicant's argument that the invention concerns polyepitope constructs that contain two or more appropriate CTL epitopes lacking naturally occurring flanking sequences or methionine residues wherein the polyepitope protein is successfully processed, the claims are not drawn to a method of processing of polyepitope protein comprising CTL epitopes lacking naturally occurring flanking sequences or methionine residues.

There is insufficient written description about the structure of any polynucleotide and nucleic acid vaccine because the "CTL epitopes" and "intervening sequence" without the nucleotide sequence or SEQ or amino acids sequence have no structure, much less function. Further, the term "comprise" is open-ended. It expands the intervening sequence to include additional nucleotide at either of both ends. Not only the number of CTL epitope is not defined in claim 14, the term "comprising" is open-ended. It expands the polynucleotide to include additional nucleotides at either or both ends of the undisclosed CTL epitopes from a host of undisclosed pathogens. Further the "intervening sequence that does not comprise a methionine" as disclosed in the specification refers to the internal initiation sequence (i.e. the codon ATG associated with a Kozac sequence) between **nucleotide sequences** encoding each CTL epitope. Because the internal initiation sequence is omitted, the resulting polynucleotide encoding the

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fusion protein comprises a plurality of cytotoxic T epitopes encoded by the polynucleotide having the internal translation initiation sequences omitted should be contiguous and **not spaced apart** by any intervening sequence as recited in claim 14. Since the polynucleotide encoding any CTL epitopes is inadequately described, it follows that any vector and any nucleic acid vaccine comprising any undisclosed polynucleotide is not adequately described for use as a vaccine against pathogen such as HIV.

7. Claims 14-34 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claims 14-34 as written represent a departure from the specification and the claims as originally filed because the specification on page 2, lines 10-16 (now paragraph 6 of the substitute specification) and the claims as originally filed require that at least the polynucleotide including at least one sequence encoding a plurality of cytotoxic T lymphocyte epitopes from one or more pathogens and wherein the at least one sequence is **"substantially free of sequences encoding peptide sequences naturally found to flank the CTL epitopes"**.

Applicants' arguments filed 11/25/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 52 and 67 have been amended to recite "each CTL epitope is substantially free of peptide sequences naturally found to flank that CTL epitopes". (2) It is clear that the specification did not intend the list of vectors provided at page 3 of the specification to be exhaustive. The enclosed Cox Declaration (Appendix F) supports the conclusion that the skilled artisan would have been aware at the filing date of a different viral vectors and that any known viral vector could be successfully used in the context of the present invention.

The amended Claim 14 still recites "...CTL epitopes are contiguous or space apart by intervening sequences wherein said intervening sequences do not (i) comprise methionine or (ii) comprises naturally occurring flanking sequences of the epitopes". Claims 15-32 are included in this rejection because they depend on rejected claim 14. Likewise, the amended Claim 33 still recites "...CTL epitopes are contiguous or **space apart by an intervening sequence** that does do

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not (i) comprise methionine". Claim 34 is included in this rejection because it depends on rejected claim 33.

With regard to claim 21, the specification does not have support for the term "Viral vector".

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Whitton et al *et al.* (of record, J. Virology 67(1): 348-352, January 1993; PTO 892).

Whitton *et al.* teach a polynucleotide encoding a plurality of CTL epitopes such as two CTL epitopes (MG3 and MG4) from lymphocytic choriomeningitis virus (LCMV) in an expression vector (VVMG34) wherein said vector is a viral vector from vaccinia virus (See page 349, left column Materials and Methods; page 349 right column, page 350 Fig. 2, in particular). The reference further teaches a nucleic acid comprising said polynucleotide encoding two CTL epitopes in a vaccinia virus vector which is administered to mice (See page 349, col. 1, paragraph 1 and col. 2, paragraph 2 and 3, in particular). Mice inoculated with a single dose of recombinant vaccinia vaccine are protected from a lethal dose of LCMV challenge and this protective effect is dependent upon the appropriate MHC haplotypes as demonstrated by *in vitro* CTL assays and *in vivo* protection assays (See Fig2 and Table 1, in particular). Whitton *et al.* further teach that in order to protect an outbred population such as humans; a vaccine must induce response on most if not all histocompatibility complex backgrounds to prevent the risk of vaccine failure due to nonresponder vaccinees. By using the minigene approach, it would be possible to encode up to 50 CTL epitopes in a viral vector, such as vaccinia virus (See page 351, column 1). The reference further teaches how to construct recombinant vaccinia virus carrying a polynucleotide encoding multiple CTL epitopes from peptides as short as 12 amino acid (See page 349, col. 1 Materials and Methods, in particular). The benefits of the combined vaccine confers a level of protection virtually identical to that individual vaccine alone and the protective effects of individual epitope may be enhanced in a combined vaccine (See page 351, left column). Thus, the reference teachings anticipate the claimed invention.

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Applicants' arguments filed 11/25/02 have been fully considered but are not found persuasive.

Applicants' position is that claim 15 has been amended to recite the epitopes, not the nucleic acid sequences, are contiguous.

In response, the amended claims 14-15 still recite "at least two of the plurality of CTL epitopes are contiguous or spaced by an intervening sequence that does not comprise a methionine". Further, the specification defines on page 2 at line 3-9 that "substantially free of sequences naturally found to flank the cytotoxic T lymphocyte epitopes is to be taken as including such short lengths (e.g. 1-5 amino acids) of sequences naturally found to flank the cytotoxic T lymphocyte epitopes". Finally, the term "comprise" is open-ended. It expands the intervening sequence to include additional nucleotide at either or both ends of the intervening sequence. The term "comprising" is open-ended. It expands the CTL epitope to include additional amino acid residues at either or both ends.

10. Claims 14-16, 20-22, 25, 27 and 33-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Lawson et al (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892).

Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full length inherently contains more than one CTL epitope) derived from a pathogen wherein the pathogen is **influenza** virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 11/25/02 have been fully considered but are not found persuasive.

Applicants' position is that claims 14 and 33 have been amended to recite each CTL epitopes is substantially free of peptide sequences naturally found to flank that CTL epitopes".

However, the amended claims 14 and 33 still recite "at least two of the plurality of CTL epitopes are contiguous or spaced by an intervening sequence that does not comprise a methionine". Further, the specification defines on page 2 at line 3-9 that "substantially free of sequences naturally found to flank the cytotoxic T lymphocyte epitopes is to be taken as including such short lengths (e.g. 1-5 amino acids) of sequences naturally found to flank the cytotoxic T lymphocyte epitopes". Finally, the term "comprise" is open-ended. It expands the intervening sequence to include additional nucleotide at either or both ends of the intervening

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sequence. The term "comprising" is open-ended. It expands the CTL epitope to include additional amino acid residues, the corresponding nucleotide at either or both ends.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 14 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Whitton *et al.* (of record, J. Virology 67(1): 348-352, January 1993; PTO 892).

Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full length inherently contains more than one epitope) derived from a pathogen wherein the pathogen is **influenza** virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous.

The claimed invention as recited in claims 14, 17-19 differs from the reference only by the recitation of said polynucleotide encoding 3, 9 or 10 CTL epitopes.

Whitton *et al.* teach a polynucleotide **comprising** two CTL epitopes (MG3 and MG4) from lymphocytic choriomeningitis virus (LCMV) in an expression vector (VVMG34) wherein said vector is a viral vector from vaccinia virus (See page 349, left column Materials and Methods; page 349 right column, page 350 Fig. 2, in particular). The reference further teaches a



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nucleic acid comprising said polynucleotide encoding two CTL epitopes in a vaccinia virus vector which is administered to mice (See page 349, col. 1, paragraph 1 and col. 2, paragraph 2 and 3, in particular). Mice inoculated with a single dose of recombinant vaccinia vaccine are protected from a lethal dose of LCMV challenge and this protective effect is dependent upon the appropriate MHC haplotypes as demonstrated by *in vitro* CTL assays and *in vivo* protection assays (See Fig2 and Table 1, in particular). Whitton *et al.* further teach that in order to protect an outbred population such as humans; a vaccine must induce response on most if not all histocompatibility complex backgrounds to prevent the risk of vaccine failure due to nonresponder vaccinees. By using the minigene approach, it would be possible to encode up to 50 CTL epitopes in a viral vector, such as vaccinia virus (See page 351, column 1). The reference further teaches how to construct recombinant vaccinia virus carrying a polynucleotide encoding multiple CTL epitopes from peptides as short as 12 amino acid (See page 349, col. 1 Materials and Methods, in particular). The benefits of the combined vaccine confers a level of protection virtually identical to that individual vaccine alone and the protective effects of individual epitope may be enhanced in a combined vaccine (See page 351, left column). Whitton *et al* teach that the protective effects of individual epitopes may by synergistic and the combination vaccine confers a level of protection virtually identical to that by individual epitope alone (See Whitton et al, page 351, left column 1, in particular). From the teaching of Whitton as discussed supra, it is apparent that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention because Whitton *et al* teach that polynucleotide can encode up to 50 CTL epitopes (See page 351, column 1).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add additional CTL epitopes as taught by Whitton et al to the contiguous CTL epitopes as taught by Lawson et al.

One having ordinary skill in the art would have been motivated to prepare recombinant vaccinia vaccine containing 3, 9 and 10 CTL epitopes because the benefit of having multiple CTL epitopes in a single vaccine would improve vaccine coverage in a population having heterogeneous MHC genetic backgrounds as taught by Whitton *et al.*

Applicants' arguments filed 11/25/02 have been fully considered but are not found persuasive.

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Applicants' position is that claims 14 and 33 have been amended to recite each CTL epitopes is substantially free of peptide sequences naturally found to flank that CTL epitopes".

However, the amended claims 14 and 33 still recite "at least two of the plurality of CTL epitopes are contiguous or spaced by an intervening sequence that does not comprise a methionine". Further, the specification defines on page 2 at line 3-9 that "substantially free of sequences naturally found to flank the cytotoxic T lymphocyte epitopes is to be taken as including such short lengths (e.g. 1-5 amino acids) of sequences naturally found to flank the cytotoxic T lymphocyte epitopes". Finally, the term "comprise" is open-ended. It expands the intervening sequence to include additional nucleotide at either or both ends of the intervening sequence. The term "comprising" is open-ended. It expands the CTL epitope to include additional amino acid residues, the corresponding nucleotide at either or both ends.

14. Claims 14 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) and Whitton *et al.* (of record, J. Virology 67(1): 348-352, January 1993; PTO 892) in view of Berzofsky *et al.* (of record, U.S. Patent No. 5,980,899; PTO 892) for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) ) Lawson et al disclose not two CTL epitopes present in a single construct, but one epitope and the signal sequence from adenovirus E//19K glycoprotein.

However, Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full length inherently contains more than one epitope) derived from a pathogen wherein the pathogen is **influenza** virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous.

The teachings of Lawson et al and Whitton et al have been discussed supra.

The claimed invention in claim 26 differs from the references only by reciting polynucleotide encodes CTL epitopes from a plurality of pathogens.

Berzofsky *et al* teach recombinant vaccinia virus expressing a polynucleotide encoding cytotoxic T cell (CTL) epitopes from hepatitis C virus NS5, vSC8, vSC25 and HIV-1gp 160 (See column 18, line 39; column 19, line 29 in particular) and chronic infection is of medically important problem (see column 1 line 65 bridging column 2, line 10).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make and use CTL epitopes from multiple pathogens as taught by Berzofsky *et al* for a recombinant combination vaccine as taught by Lawson *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One of ordinary skill in the art at the time the invention was made would have been motivated to use CTL epitopes from multiple pathogens taught by Berzofsky for a recombinant combination vaccine as taught by Lawson *et al* because the protective effects of individual epitopes may be synergistic and the combination vaccine confers a level of protection virtually identical to that by individual epitope alone as taught by Whitton *et al* (See Whitton *et al*, page 351, left column 1, in particular).

Applicants' arguments filed 11/25/02 have been fully considered but are not found persuasive.

Applicants' position is that claims 14 and 33 have been amended to recite each CTL epitopes is substantially free of peptide sequences naturally found to flank that CTL epitopes".

However, the amended claims 14 and 33 still recite "at least two of the plurality of CTL epitopes are contiguous or spaced by an intervening sequence that does not comprise a methionine". Further, the specification defines on page 2 at line 3-9 that "substantially free of sequences naturally found to flank the cytotoxic T lymphocyte epitopes is to be taken as including such short lengths (e.g. 1-5 amino acids) of sequences naturally found to flank the cytotoxic T lymphocyte epitopes". Finally, the term "comprise" is open-ended. It expands the intervening sequence to include additional nucleotide at either or both ends of the intervening sequence. The term "comprising" is open-ended. It expands the CTL epitope to include additional amino acid residues, the corresponding nucleotide at either or both ends.

15. Claims 14, 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (J Virology 68(6): 3505-3511, June 1994, PTO 892, see entire document) in view of Del Val *et al* (of record, J. Virology 65(7): 3641-3646, July 1991; PTO 892) or Latron *et al* (of record, Proc. Natl. Acad. Sci. USA 88: 11325-11329, Dec 1991; PTO 892) or Burrows *et al* (of record, J. General Virology 75: 2489-2493, 1994; PTO 892).

The teachings of Lawson *et al* have been discussed supra.

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The claimed invention as recited in claims 14, 17-19 differs from the references only by the recitation of said polynucleotide encoding 3, 9 or 10 CTL epitopes.

The reference teachings differ from the claimed invention by not using CTL epitopes from cytomegalovirus or influenza virus or Epstein-Barr virus.

Del Val *et al* teach CTL epitopes from cytomegalovirus and a recombinant vaccine against lethal CMV infection (See page 3641, Materials and Methods; page 3643, Fig. 2, in particular).

Latron *et al* teach CTL epitopes from Influenza by site-directed mutagenesis of genomic DNA (See page 11325, Materials and Methods; page 11326, Table 1, in particular). Latron *et al* further teach that mutation in the amino residues at 114 and 116 can abolish CTL immune response against Influenza (See Table 1, in particular).

Burrows *et al.* teach five new CTL epitopes of Epstein-Barr virus (See table 1, in particular) and EBV infection appears to be common in Western societies and there is appears to be 50% chance of developing infectious mononucleosis (See page 2489, column 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the CTL epitopes from cytomegalovirus as taught by Del Val *et al* or the CTL epitope from Influenza as taught by Latron *et al* or the CTL epitopes of Epstein-Barr virus as taught by Burrows *et al* with the CTL epitope from LCMV as taught by Whitton *et al* or the CTL epitope as taught by Lawson *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One having ordinary skill in the art would have been motivated to substitute the CTL epitopes from CTL epitope from Influenza taught by Lawson *et al* with the CTL epitopes from CMV taught by Del Val *et al* or CTL epitopes from Influenza taught by Latron *et al* or CTL epitopes of Epstein-Barr virus taught by Burrows *et al* for a vaccine comprises CTL epitopes from a pathogen for a vaccine taught by Lawson *et al* with the expectation that the vaccine using CTL epitopes from the CTL epitope from Influenza taught by Lawson *et al* would also have the same protective effect when substitute CTL epitopes from other pathogens such as cytomegalovirus, Influenza or Epstein-Barr virus.

Applicants' arguments filed 11/25/02 have been fully considered but are not found persuasive.

Applicants' position is that claims 14 and 33 have been amended to recite each CTL epitopes is substantially free of peptide sequences naturally found to flank that CTL epitopes".

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However, the amended claims 14 and 33 still recite "at least two of the plurality of CTL epitopes are contiguous or spaced by an intervening sequence that does not comprise a methionine". Further, the specification defines on page 2 at line 3-9 that "substantially free of sequences naturally found to flank the cytotoxic T lymphocyte epitopes is to be taken as including such short lengths (e.g. 1-5 amino acids) of sequences naturally found to flank the cytotoxic T lymphocyte epitopes". Finally, the term "comprise" is open-ended. It expands the intervening sequence to include additional nucleotide at either or both ends of the intervening sequence. The term "comprising" is open-ended. It expands the CTL epitope to include additional amino acid residues, the corresponding nucleotide at either or both ends.

16. Claims 14, 20-21 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Panicali *et al* (of record, U.S. Pat No. 5,656,465, filing date May 4, 1994; PTO 892).

Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full length inherently contains more than one epitope) derived from a pathogen wherein the pathogen is influenza virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous.

The teachings of Lawson *et al* have been discussed supra.

The claimed invention in claims 14, 20-21 and 23 differs from the references only by the recitation of avipox viral vector.

Panicali *et al* teach a method of in vivo gene delivery using viral vector including, avipox (e.g. fowl pox) for delivering a wide range of genetic material (polynucleotide) (See column 3, line 21; column 7, line 3; column 11 line 17, in particular) that encode cytokines for tumor therapy (See column 4, line 28; column 5 line 31, in particular). Panicali *et al* further teach that fowl pox viruses produces abortive infection in humans and therefore do not cause disease and it can be readily be used to deliver a wide range of genetic material including multiple genes (see column 3, line 40, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the vaccinia vector as taught by Lawson *et al* with the avipox virus vector as taught by Panicali *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of

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success in producing the claimed invention. One having ordinary skill in the art would have been motivated to use avipox vector to deliver polynucleotide vaccine because the advantages of using avipox is that these viruses produce abortive infection in humans and therefore do not cause disease and they can be readily be used to deliver a wide range of genetic material including multiple genes as taught by Panicali *et al* (See column 3, line 41).

Applicants' arguments filed 11/25/02 have been fully considered but are not found persuasive.

Applicants' position is that claims 14 and 33 have been amended to recite each CTL epitopes is substantially free of peptide sequences naturally found to flank that CTL epitopes".

However, the amended claims 14 and 33 still recite "at least two of the plurality of CTL epitopes are contiguous or spaced by an intervening sequence that does not comprise a methionine". Further, the specification defines on page 2 at line 3-9 that "substantially free of sequences naturally found to flank the cytotoxic T lymphocyte epitopes is to be taken as including such short lengths (e.g. 1-5 amino acids) of sequences naturally found to flank the cytotoxic T lymphocyte epitopes". Finally, the term "comprise" is open-ended. It expands the intervening sequence to include additional nucleotide at either or both ends of the intervening sequence. The term "comprising" is open-ended. It expands the CTL epitope to include additional amino acid residues, the corresponding nucleotide at either or both ends.

17. Claims 14, 20-21, 24, and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Adams *et al* (of record, Intern. Rev. Immunol 11: 133-141, 1994; PTO 892).

The teachings of Lawson *et al* have been discussed supra.

The claimed invention in claims 14, 20-21, 24 differs from Lawson *et al* only by the recitation of vector wherein the vector is a virus-like particle (VLP) and the polynucleotide comprising a nucleic acid sequence encoding T and B cell epitopes as recited in Claims 29-31.

Adams *et al* teach that in order to develop vaccines that are more immunogenic than simple monomeric antigen vaccine, a polynucleotide encoding CTL epitopes to include multiple copies of T-cell and B-cell epitopes expressed in a virus-like particle (VLP) vector would enhance immune response (See page 133, Abstract, in particular). Adams *et al* further teach that VLP vector can include nucleic acid encoding polypeptide up to 43 kDa in size (See page 140, in particular).

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Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the vaccinia virus vector as taught by Lawson *et al* with the VLP viral expression vector comprising a polynucleotide encoding CTL epitopes and T helper cell and B cell epitopes as taught by Adams *et al* to enhance CTL response. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One having ordinary skill in the art would have been motivated to make a polynucleotide encoding CTL epitopes to include T helper cell and B cell epitopes because T helper cell would enhance cytokine production while B cell epitopes would induce humoral immune response along with potent CTL immune response in the absence of adjuvant. One having ordinary skill in the art would substitute the vaccinia vector as taught by Lawson *et al* with the VLP vector as taught by Adams because its versatility in packing nucleic acid encoding polypeptide up to 43 kDa in size (See page 140, in particular).

Applicants' arguments filed 11/25/02 have been fully considered but are not found persuasive.

Applicants' position is that claims 14 and 33 have been amended to recite each CTL epitopes is substantially free of peptide sequences naturally found to flank that CTL epitopes".

However, the amended claims 14 and 33 still recite "at least two of the plurality of CTL epitopes are contiguous or spaced by an intervening sequence that does not comprise a methionine". Further, the specification defines on page 2 at line 3-9 that "substantially free of sequences naturally found to flank the cytotoxic T lymphocyte epitopes is to be taken as including such short lengths (e.g. 1-5 amino acids) of sequences naturally found to flank the cytotoxic T lymphocyte epitopes". Finally, the term "comprise" is open-ended. It expands the intervening sequence to include additional nucleotide at either or both ends of the intervening sequence. The term "comprising" is open-ended. It expands the CTL epitope to include additional amino acid residues, the corresponding nucleotide at either or both ends.

18. Claims 14 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Celis *et al* (of record, Proc. Natl. Acad. Sci USA 91: 2105-2109, March 1994; PTO 892).

The teachings of Lawson *et al* have been discussed *supra*.

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The claimed invention recited in claims 14 and 28 differs from the references teachings only by the recitation of CTL epitope from tumor.

Celis *et al* teach immunotherapy for melanoma using CTL epitopes from tumor such as MAGE-1, MAGE-2, and MAGE from melanoma for cancer vaccine (See abstract and Table 1; page 2109, last paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to reverse transcribe the CTL epitopes from tumor as taught by Celis *et al* before substitute with the polynucleotide encoding the CTL epitope from Influenza as taught by Lawson *et al* for a cancer vaccine. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One having ordinary skill in the art would have been motivated to use tumor epitopes as taught by Celis *et al* for a cancer vaccine using the approach as taught by whitton which would prevent the risk of vaccine failure due to nonresponder vaccinees.

Applicants' arguments filed 11/25/02 have been fully considered but are not found persuasive.

Applicants' position is that claims 14 and 33 have been amended to recite each CTL epitopes is substantially free of peptide sequences naturally found to flank that CTL epitopes".

However, the amended claims 14 and 33 still recite "at least two of the plurality of CTL epitopes are contiguous or spaced by an intervening sequence that does not comprise a methionine". Further, the specification defines on page 2 at line 3-9 that "substantially free of sequences naturally found to flank the cytotoxic T lymphocyte epitopes is to be taken as including such short lengths (e.g. 1-5 amino acids) of sequences naturally found to flank the cytotoxic T lymphocyte epitopes". Finally, the term "comprise" is open-ended. It expands the intervening sequence to include additional nucleotide at either or both ends of the intervening sequence. The term "comprising" is open-ended. It expands the CTL epitope to include additional amino acid residues, the corresponding nucleotide at either or both ends.

19. Claims 14 and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Widmann *et al* (of record, J Immunol Method 155: 95-99, 1992; PTO 892).

The teachings of Lawson *et al* have been discussed supra.



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The claimed invention recited in claims 14 and 29-30 differs from the references teachings only by the recitation of said polynucleotide encoding CTL epitopes, including T helper cell epitope.

Widmann *et al* teach T helper cell epitopes from *P. berghei* and *Plasmodium yoelii* (see page 96, col. 1, paragraph 1 and page 97, col. 2, paragraph 1, in particular) are linked to the CTL epitope (DSYIPSAEKI) in tandem in order to enhance the cytotoxic response of mice (See page 96, col. 2 Results and Discussion, page 97 col. 2, paragraph 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to reverse transcribe the T helper epitopes as taught by Widmann *et al* before linking the polynucleotide encoding said T helper epitopes to the polynucleotide encoding the CTL epitope from Influenza virus as taught by Lawson *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One having ordinary skill in the art would have been motivated to make polynucleotide encoding CTL epitopes together with T helper cell epitopes because T helper cell epitope has been shown to enhance the CTL as taught by Widmann *et al*.

Applicants' arguments filed 11/25/02 have been fully considered but are not found persuasive.

Applicants' position is that claims 14 and 33 have been amended to recite each CTL epitopes is substantially free of peptide sequences naturally found to flank that CTL epitopes".

However, the amended claims 14 and 33 still recite "at least two of the plurality of CTL epitopes are contiguous or spaced by an intervening sequence that does not comprise a methionine". Further, the specification defines on page 2 at line 3-9 that "substantially free of sequences naturally found to flank the cytotoxic T lymphocyte epitopes is to be taken as including such short lengths (e.g. 1-5 amino acids) of sequences naturally found to flank the cytotoxic T lymphocyte epitopes". Finally, the term "comprise" is open-ended. It expands the intervening sequence to include additional nucleotide at either or both ends of the intervening sequence. The term "comprising" is open-ended. It expands the CTL epitope to include additional amino acid residues, the corresponding nucleotide at either or both ends.

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20. Claims 14, 29 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Potter *et al* (of record, U.S. Patent No. 5,708,155; PTO 892).

The teachings of Lawson *et al* have been discussed supra.

The claimed invention recited in claims 14, 29 and 32 differs from the references teachings only by the recitation of said polynucleotide encoding CTL epitopes, including toxin.

Potter *et al* teach that in order to increase the immunogenicity of the antigen, a DNA encoding a leukotoxin polypeptide can be fused to a selected antigen (See Abstract, in particular). The reference further teaches that leukotoxin as a carrier in a vaccine can enhance immune response of the antigens.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a polynucleotide comprising nucleic acid sequence encoding a toxin as taught by Potter and CTL epitopes for a vaccine as taught by Lawson *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One having ordinary skill in the art would have been motivated to make nucleic vaccine comprising a polynucleotide encoding CTL epitopes and toxin because the use of toxin as an adjuvant taught by Potter *et al* can improve the immune response of any vaccine such as the ones taught by Lawson *et al*.

Applicants' arguments filed 11/25/02 have been fully considered but are not found persuasive.

Applicants' position is that claims 14 and 33 have been amended to recite each CTL epitopes is substantially free of peptide sequences naturally found to flank that CTL epitopes".

However, the amended claims 14 and 33 still recite "at least two of the plurality of CTL epitopes are contiguous or spaced by an intervening sequence that does not comprise a methionine". Further, the specification defines on page 2 at line 3-9 that "substantially free of sequences naturally found to flank the cytotoxic T lymphocyte epitopes is to be taken as including such short lengths (e.g. 1-5 amino acids) of sequences naturally found to flank the cytotoxic T lymphocyte epitopes". Finally, the term "comprise" is open-ended. It expands the intervening sequence to include additional nucleotide at either or both ends of the intervening sequence. The term "comprising" is open-ended. It expands the CTL epitope to include additional amino acid residues, the corresponding nucleotide at either or both ends.

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21. Claims 14 and 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Adams *et al* (of record, Intern. Rev. Immunol 11: 133-141, 1994; PTO 892) or Potter *et al* (of record, U.S. Patent No. 5,708,155; PTO 892) or Widmann *et al* (of record, J Immunol Method 155: 95-99, 1992; PTO 892).

The teachings of Lawson *et al* have been discussed supra.

The claimed invention recited in claims 14 and 29-32 differs from the reference teachings only by the recitation of said polynucleotide encoding CTL epitopes, including T helper cell epitope, B cell epitope or Toxin.

Adams *et al* teach that in order to develop vaccines that are more immunogenic than simple monomeric antigen vaccine, a polynucleotide encoding CTL epitopes to include multiple copies of T-cell and B-cell epitopes expressed in a virus-like particle (VLP) vector would enhance immune response (See page 133, Abstract, in particular).

Widmann *et al* teach T helper cell epitopes from *P. berghei* and *Plasmodium yoelii* (see page 96, col. 1, paragraph 1 and page 97, col. 2, paragraph 1, in particular) are linked to the CTL epitope (DSYIPSAEKI) in tandem in order to enhance the cytotoxic response of mice (See page 96, col. 2 Results and Discussion, page 97 col. 2, paragraph 1, in particular).

Potter *et al* teach that in order to increase the immunogenicity of the antigen, a DNA encoding a leukotoxin polypeptide can be fused to a selected antigen (See Abstract, in particular). The reference further teaches that leukotoxin as a carrier in a vaccine can enhance immune response of the antigens.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to reverse transcribe the T helper epitopes as taught by Widmann *et al* before fusing it the polynucleotide encoding the CTL epitope from Influenza virus as taught by Lawson *et al* together with the T helper cell epitopes as taught by Widmann or the T-cell and B-cell epitopes as taught by Adams *et al* or leukotoxin as taught by Potter *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make a polynucleotide encoding CTL epitopes to include T helper cell and B cell epitopes because T helper cell would enhance cytokine production while B cell epitopes would induce humoral immune response along

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with potent CTL immune response in the absence of adjuvant as taught by Adams *et al.* Widmann *et al.* teach T helper cell epitope has been shown to enhance the CTL as taught by Widmann *et al.*

Applicants' arguments filed 11/25/02 have been fully considered but are not found persuasive.

Applicants' position is that claims 14 and 33 have been amended to recite each CTL epitopes is substantially free of peptide sequences naturally found to flank that CTL epitopes".

However, the amended claims 14 and 33 still recite "at least two of the plurality of CTL epitopes are contiguous or spaced by an intervening sequence that does not comprise a methionine". Further, the specification defines on page 2 at line 3-9 that "substantially free of sequences naturally found to flank the cytotoxic T lymphocyte epitopes is to be taken as including such short lengths (e.g. 1-5 amino acids) of sequences naturally found to flank the cytotoxic T lymphocyte epitopes". Finally, the term "comprise" is open-ended. It expands the intervening sequence to include additional nucleotide at either or both ends of the intervening sequence. The term "comprising" is open-ended. It expands the CTL epitope to include additional amino acid residues, the corresponding nucleotide at either or both ends.

22. The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timeless extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cirri. 1993); *In re Long*, 759 F.2d 887, 225 USPQ 645 (Fed. Cirri. 1985); *In re Van Onramp*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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23. Claims 14-34 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 14-35 of USSN 09/957,107.

(1) Claim 14 of USSN 09576,107 recites a polynucleotide comprising a nucleic acid sequences encoding at least two CTL epitopes wherein at least two of the epitopes are restricted by the same HLA gene. Therefore, claim 14 of USSN 09576,107 is included in the instant claims 14-15 which drawn to a polynucleotide comprising a nucleic acid sequence encoding a plurality of CTL epitopes, wherein at least two of the sequences encoding said CTL epitopes are contiguous or spaced apart by intervening sequence do not (i) comprise methionine or (ii) encode naturally occurring flanking sequences of the epitopes as recited in claim 14 of instant application. Note, although Claim 14 of USSN 09576,107 does not explicitly claim the CTL epitopes are contiguous or spaced apart and claim 14 of instant application does not explicitly claim the said epitopes are restricted by the same HLA gene, since all CTL epitopes are from MHC class I, the spacing between epitopes is an obvious variation of the recombinant fusion protein. Further, the recitation of "at least two CTL epitopes" in claim 14 of USSN 09576,107 is an obvious variation of "a plurality of CTL epitopes" as recited in instant claim 14.

(2) Claims 15-34 of USSN 09576,107 are the same as that recited in the instant claims 15-32.

(3) Claim 35 of USSN 09576,107 recites a nucleic vaccine comprising a polynucleotide comprising a nucleic acid sequence encoding at least two CTL epitopes from one or more pathogens, wherein at least two of said epitopes are restricted by the same HLA gene and an acceptable carrier which is included in the claims 33 and 34 of instant application since claim 33 of instant application recites a nucleic acid vaccine comprising a polynucleotide comprising a nucleic acid sequence encoding a plurality of CTL epitopes, wherein at least two of said CTL epitopes are contiguous or spaced apart by intervening sequences, wherein said intervening sequences do not (i) comprise an initiation codon or (ii) encode naturally occurring flanking sequences of the epitopes, and an acceptable carrier and claim 34 of instant application recites a nucleic acid vaccine comprising a polynucleotide comprising a nucleic acid sequence encoding a plurality of CTL epitopes, wherein the sequences encoding said CTL epitopes are contiguous and an acceptable carrier. Since the claims of instant application include the invention of USSN 09576,107, issuance of a patent to the instant application would improperly extend the right to exclusivity. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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It is noted that Applicants will respond by submission of an appropriate terminal disclaimer upon the event that conflicting claims issue from USSN 09/576,107 and the present application; the rejection is maintained.

24. No claim is allowed.
25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.
26. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.  
Patent Examiner  
Technology Center 1600  
March 24, 2003

*Phillip Gambel*  
PHILLIP GAMBEL, PH.D  
PRIMARY EXAMINER  
*TECH CENTER 1600*  
*3/24/03*